REMARKS

Claims 1 to 31, 35, 36, 38 and 39 are pending in the application. Claims 32 to 34 and 37 have been withdrawn in response to the Restriction Requirement.

Claim amendment

The independent claims have been amended to recite "wherein said co-amplifying is stopped during an exponential phase of the co-amplification". This amendment is supported in the original application, for example at page 15, lines 4 to 7 and page 20, lines 11 to 13.

Claim Interpretation

In the Office Action, it is indicated that the "sequential dispensation order of individual nucleotides" is interpreted as performing the steps of "pyrosequencing". Applicant respectfully disagrees. In the process of "pyrosequencing", each nucleotide (either A, C, G or T) is dispensed in a sequential order such as only one nucleotide is present at a time in the reaction solution. The term "pyro" relates to the release of pyrophosphate upon the incorporation of a nucleotide in a DNA fragment during elongation. The released pyrophosphate is then used to create light and therefore detect incorporation of the dispensed nucleotide. This method of sequentially dispensing individual nucleotides is contemplated by Applicant as an embodiment of the method presently claimed (claims 6 to 8). However, Applicant respectfully submits that the sequential dispensation order of individual nucleotides other than the "pyrosequencing" process, such as the Helicos™ sequencer, are also contemplated. In the latter, sequential dispensation of individual fluorescently labeled nucleotides are used in the process of sequencing. This alternative technology is evidenced by the abstract of the Harris et al. publication (Single-Molecule DNA Sequencing of a Viral Genome, Science 4 April 2008: Vol. 320. no. 5872, pp. 106 – 109):

> "The full promise of human genomics will be realized only when the genomes of thousands of individuals can be sequenced for comparative analysis. A reference sequence enables the use of short read length. We report an amplification-free method for determining the nucleotide sequence of more than 280,000 individual DNA molecules simultaneously. A DNA polymerase adds labeled nucleotides to surface-immobilized primer-template duplexes in stepwise fashion, and the asynchronous growth of individual DNA molecules was monitored by fluorescence imaging. Read lengths of >25 bases and equivalent phred software program quality scores approaching 30 were achieved. We used this method to sequence the M13 virus to an average depth of >150x and with 100% coverage; thus, we resequenced the M13 genome with high-sensitivity mutation detection. This demonstrates a strategy for high-throughput low-cost resequencing".

As such, Applicant respectfully considers that the "sequential dispensation order of individual nucleotides" is not limited to the Pyrosequencing™ process.

Claims Rejections – 35 U.S.C. § 103

Claims 1 to 9, 15 to 26 and 35 to 39 have been rejected for allegedly being obvious to a person skilled in the art in view of Antonarakis et al. Applicant respectfully disagrees and requests reconsideration on the following grounds.

Applicant respectfully submits that Antonorakis et al. fails to teach or suggest stopping the co-amplifying step during an exponential phase of a co-amplification. Instead, in order to detect chromosomal abnormalities, Antonorakis et al. relies on the amplification of highly identical sequences and on a substantially similar amplification efficiency for the first and the second amplification products to quantify the relative amount of the first sequence. To this end, the Examiner is referred to paragraph [0012] of Antonorakis et al.:

> "Preferably, the first and second sequence are paralogous sequences located on different chromosomes, although in some aspects, they are located on the same chromosome (e.g., on different arms). The first and second amplification products comprise greater than about 80% identity, and preferably, are substantially identical in length. Because the amplification efficiency of the first and second sequences is substantially the same, the method is highly quantitative and reliable" [emphasis added].

At paragraphs [0060] to [0065], Antonorakis et al. thoroughly describe how to identify paralogous genes and their importance in selecting the appropriate one for the determination of chromosomal abnormalities. By emphasizing the importance of paralogous genes as a control (or second sequence) in the determination of chromosomal abnormalities, Antonorakis et al. fails to teach to those skilled in the art that an unrelated control (e.g. second) sequence be used.

As such, Antonorakis et al. is thus clearly relying on the similarity between the first and second sequence to preserve substantial equal amplification efficiencies of both sequence and therefore quantify the relative amounts of the both sequences.

In contrast, in the present patent application, Applicant teaches a completely different approach to assess the amount or copy number of a known target. Applicant relies on the co-amplification of a target and a control sequence until the components (primers, nucleotides, polymerase, etc.) of the co-amplication step are not limiting the amplification itself, in order to quantify the amount of the target. Consequently, the co-amplification must be stopped during the exponential phase of the co-amplification. The method claimed herein thus relies on the termination of the co-amplification prior to the "plateau" phase of the amplification to preserve the relative amounts of the target and control sequences.

This particular limitation is absent from the teaching of Antonorakis et al. Nowhere in Antonorakis, it is indicated that the co-amplication be stopped prior to the exhaustion of the amplification components.

The approach described in the present patent application is particularly advantageous over the teaching of Antonorakis et al. First, and contrary to Antonorakis et al., the method is not limited by the degree of identity between the target and the control sequences. Second, the method is not limited to amplifications products that are similar in length or that have similar

amplification efficiencies. Third, the method can easily be accommodated by using two pairs of primers having little or no identity between one another. Fourth, the method can be used for the determination of more than one target sequence.

In light of the above, Applicant respectfully submits that the claims are compliant with 35 U.S.C. 103 and respectfully requests reconsideration.

Claims 10 to 14 have been rejected for allegedly being obvious to a person skilled in the art in view of Antonarakis et al. and further in view of Pourmand et al.

Applicant respectfully disagrees. As indicated above, Antonorakis et al. fails to teach or suggest that the co-amplification step be stopped during the exponential phase of the amplification. Applicant further submits that Pourmand et al. also fails to teach this limitation. First, Pourmand et al. determine the presence/absence of alleles concurrently at more than one locus in the a single reaction. Pourmand et al. assessment is thus a qualitative one. There is no indication in Pourmand et al. to stop the co-amplification step during the exponential phase of the amplification.

Contrary to Pourmand et al., the method presently claimed sequentially determines the amounts or the target and of the control. Also in contradiction with Pourmand et al., the method presently claimed enables the quantitative assessment of a target sequence.

The main advantages of the method described herein over Pourmand et al. are the following:

- In the target or the control sequences, no SNPs or polymorphism are required, as the exact sequence of both the target and the control is not important.
- The method is quantitative and enables the assessment of the relative amount of the target sequence with respect to the control sequence.

Because the teaching of Pourmand et al. fails to complement the teaching of Antonorakis et al., Applicant respectfully submits that the claims are compliant with 35 U.S.C. 103. Reconsideration is thus respectfully requested.

Concluding Remarks

Applicant respectfully submits that no new matter has been added by the present amendments.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 1 to 31, 35, 36, 38 and 39 at an early date is solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Should any fee deficiencies be associated with this submission, the Commissioner is authorized to debit such deficiencies to the Nixon Peabody Deposit Account No. 50-0850. Any overpayments should be credited to said Deposit Account.

Respectfully submitted,

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